

made to 'identify' target/ligand interactions using the method steps as taught by Kim et al. in conjunction with the mass spectrometer techniques as taught by Siuzdak because Siuzdak explicitly shows that the technique can be applied to both 'covalent' and 'non-covalent' including antibody-antigen interactions." The Examiner further states that "one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray "demonstrated its potential" for these systems," and since Siuzdak allegedly "discloses that BOTH 'covalent' and 'non-covalent' interactions can be measured (and distinguished) using a mass spectrometer." (Emphasis original.) Finally, the Examiner notes that "one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen."

In rebuttal of the rejections, enclosed is a Declaration of Gary Siuzdak, Ph.D., the sole author of the secondary reference, cited in support of the outstanding rejections.

As stated in the Declaration, Dr. Siuzdak is currently the Senior Director at the Center for Mass Spectrometry and Associate Professor of Molecular Biology at The Scripps Institute.

According to paragraphs 3 and 4, Dr. Siuzdak disagrees with the Examiner's conclusion that his statement that "[e]lectrospray ionization mass spectrometry has also demonstrated its potential . . . for observing covalent protein-bound intermediates in an antibody-catalyzed reaction" would have motivated one skilled in the art to identify a novel ligand by the mass spectrometry detection of a covalently bound protein-ligand conjugate in a mixture."

As Dr. Siuzdak explains in paragraph 5, studies of enzymatic mechanisms, like those disclosed in the cited portion of his book, "involve the detailed characterization of a single reaction where the participants, namely an enzyme and its substrate, are known."

In paragraph 6, Dr. Siuzdak goes on explaining that "[w]hile electrospray ionization mass spectrometry is well suited to study enzymatic mechanisms where all of the participants are known, its use to analyze mixtures of unknown components is limited." One reason for this is that "heterogeneous compounds can produce complicated spectra that can be difficult or impossible to interpret." Another obstacle is that "heterogeneous mixtures tend to reduce the

sensitivity of electrospray ionization mass spectrometry." Dr. Siuzdak adds that "these obstacles are shared by other techniques of mass spectrometry."

In view of the foregoing explanation, in paragraph 7 Dr. Siuzdak states: "I do not believe that a person skilled in the art would have assumed that the mass spectrometry techniques to study enzymatic mechanisms would have been applicable to identify novel ligand by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected."

Applicants note that a Declaration in which the sole author of a reference necessary to support a rejection directly contradicts the Examiner's reading of his statements and the conclusions drawn from such statements, has a high probative value. Accordingly, the Examiner is respectfully requested to reconsider and withdrawn the outstanding rejections.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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Panpan Gao
Reg. No. 43,626

HELLER EHRLICH WHITE & McAULIFFE LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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